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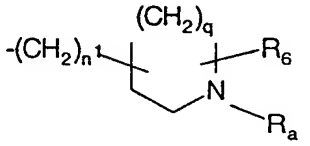
(54) Title: PIPERIDINE DERIVATIVES AS 5-HT4 RECEPTOR ANTAGONISTS



(II)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof: X-CO-Y-Z, wherein X is a monocyclic or polycyclic aromatic group, Y is O or NH; Z is of sub-formula (II), wherein $-(CH_2)_{n^1}$ is attached at carbon; and n^1 is 0, 1, 2, 3 or 4; q is 0, 1, 2 or 3; R_a is straight or branched chain alkylene of chain length 1-6 carbon atoms terminally substituted by R_7 wherein R_7 is aryl, 3 to 8 membered cycloalkyl, 3 to 8 membered heterocyclyl, 5 or 6 membered monocyclic heteroaryl or 9 or 10 membered fused bicyclic heteroaryl linked through carbon, or R_7 is C_{2-7} alkoxycarbonyl or secondary or tertiary hydroxy substituted C_{1-6} alkyl; and R_6 is hydrogen or C_{1-6} alkyl; or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere; and their use as pharmaceuticals in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

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PIPERIDINE DERIVATIVES AS 5-HT4 RECEPTOR ANTAGONISTS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited), WO 93/02677, WO 93/03725, WO 93/05038, WO 93/05040 and WO 93/18036 (SmithKline Beecham plc) describe compounds having 5-HT_4 receptor antagonist activity.

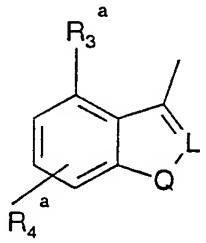
It has now been discovered that certain novel compounds also have 5-HT_4 receptor antagonist properties.

Accordingly, the present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

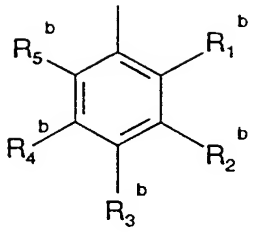
X-CO-Y-Z (I)

wherein

X is a monocyclic or polycyclic aromatic group, such as a group of formula (a), (b), (c), (d), (e), (f) or (g):



(a)



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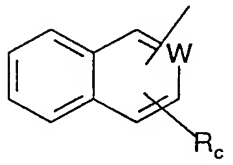

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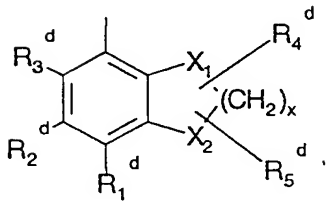

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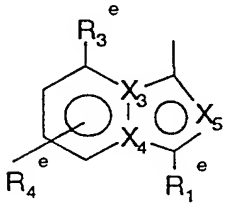

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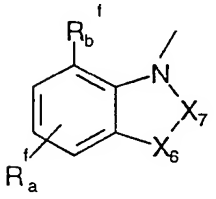

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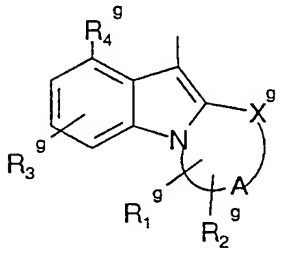


(g)

wherein

L is N or CR_S wherein R_S is hydrogen, C_{1-6} alkoxy, halogen, C_{1-4} alkyl or cyano;

Q is NR_1^a, CH_2, O or S;

W is CH or N;

in which X_1-$(CH_2)_x$-X_2 forms a 5-7 membered ring wherein X_1 is O or S; X_2 is O, S, NR or NRCO wherein R is hydrogen or C_{1-6} alkyl; and

x is 1, 2 or 3;

one of X_3 and X_4 is N and the other is C; and

X_5 is N or CR wherein R is hydrogen, C_{1-6} alkoxy, halo, C_{1-6} alkyl or cyano;

R_1^a is hydrogen, C_{1-10} alkyl, C_{2-6} alkenyl, aralkyl, C_{2-6} alkanoyl or C_{2-6} alkanoyl C_{1-3} alkyl;

R_3^a is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkoxy;

R_4^a is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R_1^b is C_{1-6} alkoxy; and

R_2^b is hydrogen, chloro or fluoro;

R_3^b is hydrogen,C_{1-6} alkyl, amino optionally substituted by a C_{1-6} alkyl group, halo, hydroxy or C_{1-6} alkoxy;

R_4^b is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio; and

R_5^b is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_c is hydrogen, C_{1-6} alkoxy, halo or C_{1-6} alkyl;

R_1^d is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2^d is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3^d is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4^d and R_5^d are independently hydrogen or C_{1-6} alkyl;

R_1^e is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkyl C_{1-4} alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups;

R_3^e is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkyl;

R_4^e is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

X_6-X_7 is NR_z-CO or $CR_1^fR_2^f$-$CR_3^fR_4^f$ where

R_z and R_1^f to R_4^f are independently hydrogen or C_{1-6} alkyl; and/or

R_1^f/R_2^f and R_3^f/R_4^f together are a bond and/or $R_1^f/R_2^f/R_3^f/R_4^f$ are joined to form C_{3-6} polymethylene;

R_a^f is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkyl;

R_b^f is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

X^g is O, S, SO, SO_2, CH_2, CH, N or NR wherein R is hydrogen or C_{1-6} alkyl;

A is a saturated or unsaturated polymethylene chain of 2 - 4 carbon atoms;

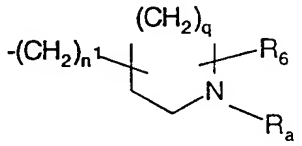
R_1^g and R_2^g are hydrogen or C_{1-6} alkyl;

R_3^g is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkoxy;

R_4^g is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

Y is O or NH;

Z is of sub-formula:



wherein

$-(CH_2)_n^1$ is attached at carbon; and

n^1 is 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

R_a is straight or branched chain alkylene of chain length 1-6 carbon atoms terminally substituted by R_7 wherein and R_7 is aryl, 3 to 8 membered cycloalkyl, 3 to 8 membered heterocyclyl, 5 or 6 membered monocyclic heteroaryl or 9 or 10 membered fused bicyclic heteroaryl linked through carbon, or R_7 is C_{2-7} alkoxycarbonyl or secondary or tertiary hydroxy substituted C_{1-6} alkyl; and

R_6 is hydrogen or C_{1-6} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

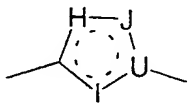
in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

Examples of alkyl or alkyl containing groups include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} or C_{12} branched, straight chained or cyclic alkyl, as appropriate. C_{1-4} alkyl groups include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl optionally substituted by one of more alkyl groups of up to 4 carbon atoms.

Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy.

Halo includes fluoro, chloro, bromo and iodo, preferably chloro.

A suitable bioisostere for the amide or ester linkage containing Y in formula (I), is of formula:



wherein

the dotted circle represents one or two double bonds in any position in the 5-membered ring; H, J and I independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of H, J and I is other than carbon; U represents nitrogen or carbon.

Suitable examples of bioisosteres are as described for X, Y and Z in EP-A-328200 (Merck Sharp & Dohme Ltd.), such as an oxadiazole moiety.

L in formula (a) is favourably C-H, C-CH_3, C-Cl or C-OCH_3.

Q in formula (a) is favourably $NR_1{}^a$.

$R_1{}^a$ is preferably hydrogen or a methyl or ethyl group.

$R_1{}^b$ is preferably methoxy.

$R_3{}^b$ is preferably amino.

$R_4{}^b$ is preferably halo.

$R_5{}^b$ is preferably hydrogen.

A substituent when halo is selected from fluoro, chloro, bromo and iodo. $R_4{}^a$ when halo is preferably iodo.

Suitable examples of the X_1-$(CH_2)_x$-X_2 moiety include O-$(CH_2)_2$-O, O-$(CH_2)_3$-O, O-CH_2-O, O-$(CH_2)_2$-NR, O-$(CH_2)_2$-S or O-CH_2-CONR, wherein any of the methylene linkages are optionally mono- or di- substituted by C_{1-6} alkyl groups, such as methyl. Preferably X_1-$(CH_2)_2$-X_2 is O-$(CH_2)_2$-O.

$R_1{}^d$ is preferably hydrogen or amino.

$R_2{}^d$ is preferably hydrogen or halo.

$R_3{}^d$ is preferably hydrogen or halo.

$R_4{}^d$ and $R_5{}^d$ are often hydrogen. When $R_4{}^d/R_5{}^d$ is C_{1-6} alkyl, it is often methyl. In particular $R_4{}^d$ and $R_5{}^d$ are methyl such that the disubstituent containing X_1 and X_2 is O-$C(CH_3)_2$-O.

$R_1{}^e$ is preferably CF_3 or an ethyl group.

X_5 is preferably N, C-H or C-OCH_3;

$R_3{}^e$ is preferably hydrogen.

$R_4{}^e$ is preferably hydrogen or halo, such as iodo.

Suitable examples of X_6-X_7 when $CR_1{}^fR_2{}^f$-$CR_3{}^fR_4{}^f$ include CH_2-CH_2 and CH=CH. X_6-X_7 is preferably NR_z-CO, however, such as NH-CO or NEt-CO.

$R_a{}^f$ is preferably hydrogen.

$R_b{}^f$ is preferably hydrogen or halo, such as iodo.

Values for A include $-CH_2-(CH_2)_r-CH_2-$ wherein r is 0, 1 or 2; $-CH_2-CH=CH-$; $-C(CH_3)=CH-$ or when X^g is CH or N, A may be $-(CH_2)_2-CH=$ or $-CH=CH-CH=$. Other examples of A are as described in the examples hereinafter.

R_1^g and R_2^g are often hydrogen or R_1^g and R_2^g are gem-dimethyl.

r is often 1.

R_3^g is preferably hydrogen.

R_4^g is preferably hydrogen or halo, such as fluoro.

Other suitable values of X are as described in PCT/GB93/020208, PCT/EP93/02808, PCT/EP93/02775, PCT/EP93/02809, PCT/GB93/02130 (all in the name of SmithKline Beecham plc).

Y is preferably O or NH.

n^1 is preferably 1 and the azacycle is preferably attached at a 4-position carbon atom, when q is 2.

Values of Z of interest include 4-piperidinylmethyl and 4-pyrrolidinylmethyl, N-substituted by R_a.

Values for R_7 when monocyclic heteroaryl include pyridyl, pyrimidyl, pyrazinyl, pyrryl, imidazolyl, thienyl, furanyl, oxazole or thiazole (all possible isomers). Bicyclic heteroaryl R_7 include benzofuranyl, benzothiophenyl, indolyl and indazolyl, quinolyl and *iso*quinolyl (all possible isomers).

Values for R_7 when 3 to 8 membered heterocyclyl, include cyclic polymethylene interrupted by one or two of N, O or S, linked through C or N, for example N-linked piperidinyl or pyrrolidinyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_X-T wherein R_X is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_X include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

The compounds of formula (I) wherein CO-Y is an ester or amide linkage are prepared by conventional coupling of the Z moiety with the appropriate acid. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A, EP-A-36269, EP-A-289170 and WO 92/05174 (Beecham Group p.l.c.). When CO-Y is replaced by a heterocyclic bioisostere, suitable methods are described in EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited).

The invention also comprises a process for preparing the compounds of formula (I) wherein X is of formula (d), which comprises reacting an appropriate benzoic acid derivative with an appropriate alcohol or amine. A process comprises reacting a benzoic acid derivative wherein the aromatic substituents are as required in the end compound of formula (I), or substituents convertible thereto, with an alcohol or amine containing Z or a group convertible thereto, and thereafter if necessary, converting the benzoic acid substituents and/or Z, and optionally forming a pharmaceutically acceptable salt.

Suitable examples of conversions in the aromatic substituents include chlorination of hydrogen to chloro, reduction of nitro to amino, dehydrohalogenation such as debromination, and/or elaboration of a 2,3-disubstituted benzoic acid with ethylene glycol to form the benzodioxan. Any elaboration of X is, however, usually carried out prior to ester or amide coupling.

Suitable examples of conversions in the Z containing moiety include conventional modifications of the N-substituent by substitution and/or deprotection or, in the case of a 2-, 3- or 4- substituted piperidinyl desired end compound, reduction of an appropriate pyridyl derivative.

Values for Z containing intermediates are as described in the aforementioned patent publications in the name of SmithKline Beecham plc.

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal

models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity can be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

Other CNS disorders of interest include schizophrenia, Parkinson's disease and Huntingdon's chorea.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for

example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle.

Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of irritable bowel syndrome, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of irritable bowel syndrome, gastro-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine.

The following Examples illustrates the preparation of compounds of formula (I), and the following Descriptions relate to the preparation of intermediates. The compounds of formula (I-1) and intermediates are prepared in Examples and Descriptions 1-1, 2-1 etc, the compounds of formula (I-2) are prepared in Examples and Descriptions 1-2, 2-2 etc and similarly for the compounds of formulae (I-3) to (I-5).

It will be appreciated that any compound prepared wherein Y is O may be provided as the corresponding compound wherein Y is NH.

A preferred compound corresponds to any of the compounds prepared in the Examples, but wherein there is an amino substituent in the 4-position and a chloro substituent in the 5-position of the benzoic acid nucleus depicted in formulae (I-1) to (I-5) inclusive.

Example 1 [X = (d), X_1-$(CH_2)_x$-X_2 = O-$(CH_2)_2$-O, $R_1{}^d$ = NH_2, $R_2{}^d$ = Cl, $R_3{}^d$ = H, $R_4{}^d$, $R_5{}^d$ = H; Y = O, Z = 4-piperidinylmethyl, R_a = 3-pyridylmethyl] **5-(1-(3-Pyridylmethyl)-4-piperidinyl)methyl-8-amino-7-chloro-1,4-benzodioxancarboxylate** (E1)

A stirred solution of 8-amino-7-chloro-1,4-benzodioxan-5-(4-piperidinylmethyl) carboxylate (0.1g,0.31mmol) in acetone (10ml) was treated with Et_3N (0.043ml,0.31mmol) and 3-picolyl chloride (0.043g, 0.34mmol). The reaction mixture was heated under reflux for 48 hours, cooled and evaporated *in vacuo*. The oily residue was purified by silica gel chromatography using $CHCl_3$ increasing to 2% MeOH, 98%$CHCl_3$ as eluant to yield the title compound as a pale yellow gum (0.05g) which was converted to the oxalate salt, mp 219 - 221°C.

^{1}H NMR 250MHz ($CDCl_3$) (free base)

δ : 8.60-8.40(m,2H), 7.65(d,1H), 7.50(s,1H), 7.30-7.20(m,1H), 4.45(s,2H), 4.40-4-25(m,4H), 4.10(d,2H),3.50(s,2H), 2.90(d,2H), 2.00(t,2H), 1.75(d,2H), 1.50-1.25(m,3H)

Example 2 [X = (g), X^g = O, A = $(CH_2)_3$, ($R_1{}^g$, $R_2{}^g$, $R_3{}^g$, $R_4{}^g$= H; Y = NH, Z = 4-piperidinylmethyl, R_a = 4-pyridylmethyl] **N-[(1-(4-Pyridylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide** (E2)

The title compound was prepared as an off-white solid by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 4-picolyl chloride using the procedure described in Example 1.

^{1}H NMR ($CDCl_3$)

δ: 8.55(d,2H), 8.35(d,1H), 7.10-7.40(m,5H), 6.57(t,1H), 4.55(t,2H), 4.14(t,2H), 3.51(s,2H), 3.37(t,2H), 2.80-2.98(bd,2H), 2.30-2.50(m,2H), 1.93-2.14(m,2H), 1.50-1.93(m,3H), 1.31-1.50(m,2H).

Example 3 [X = (g), X^g = O, A = $(CH_2)_3$, ($R_1{}^g$, $R_2{}^g$, $R_3{}^g$, $R_4{}^g$= H; Y = NH, Z = 4-piperidinylmethyl, R_a = 2-(1-piperidinyl)ethyl] **N-[(1-(2-(1-Piperidinyl)ethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide** (E3)

The title compound was prepared as an off-white solid by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 1-(2-chloroethyl)piperidine using the procedure described in Example 1; mp 139-141°C.

^{1}H NMR ($CDCl_3$)
δ: 8.35(d,1H), 7.07-7.48(m,3H), 6.55(t,1H), 4.56(t,2H), 4.13(t,2H), 3.35(t,2H), 2.90-3.07(bd,2H), 2.28-2.60(m,10H), 1.95-2.19(bt,2H), 1.23-1.90(m,11H).

Example 4 [X = (g), X^g = O, A = $(CH_2)_3$, (R_1^g , R_2^g, R_3^g, R_4^g= H; Y = NH, Z = 4-piperidinylmethyl, R_a = benzofuran-2-ylmethyl]
N-[(1-(Benzofuran-2-ylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (E4)

The title compound was prepared as an off-white solid by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 2-(chloromethyl)benzofuran (Blicke et al, J. Amer. Chem. Soc., 1949, 71, 2856) using the procedure described in Example 1.
^{1}H NMR ($CDCl_3$)
δ: 8.32(d,1H), 7.40-7.62(m,2H), 7.02-7.37(m,5H), 6.61(s,1H), 6.55(t,1H), 4.49(t,2H), 4.06(t,2H), 3.73(s,2H), 3.35(t,2H), 2.95-3.15(bd,2H), 2.25-2.46(m,2H), 2.02-2.25(bt,2H), 1.33-1.90(m,5H).

Example 5 [X = (g), X^g = O, A = $(CH_2)_3$, (R_1^g , R_2^g, R_3^g, R_4^g= H; Y = NH, Z = 4-piperidinylmethyl, R_a = quinolin-2-ylmethyl)]
N-[(1-(Quinolin-2-ylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (E5)

The title compound was prepared by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 2-(chloromethyl)quinoline using the procedure described in Example 1.
^{1}H NMR ($CDCl_3$)
δ: 8.32(d,1H), 8.16(d,1H), 8.08(d,1H), 7.65-7.90(m,3H), 7.54(t,1H), 7.07-7.35(m,3H), 6.58(t,1H), 4.52(t,2H), 4.09(t,2H), 3.96(s,2H), 3.35(t,2H), 3.00-3.15(m,2H), 2.25-2.50(m,4H), 1.35-1.95(m,5H).

Example 6 [X = (g), X^g = O, A = $(CH_2)_3$, (R_1^g , R_2^g, R_3^g, R_4^g= H; Y = NH, Z = 4-piperidinylmethyl, R_a = 5-phenylpentyl]

N-[(1-(5-Phenylpentyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (E6)

The title compound was prepared by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 1-chloro-5-phenylpentane using the procedure described in Example 1.

^{1}H NMR ($CDCl_3$)

δ: 8.28(d,1H), 7.08-7.30(m,8H), 6.61(t,1H), 4.54(t,2H), 4.10(t,2H), 3.34(t,2H), 3.15-3.27(bd,2H), 2.52-2.66(m,4H), 2.26-2.43(m,4H), 1.55-1.97(m,9H), 1.26-1.42(m,2H).

Example 7 [X = (g), X^g = O, A = $(CH_2)_4$, (R_1^g , R_2^g, R_3^g, R_4^g= H; Y = NH, Z = 4-piperidinylmethyl, R_a = 2-thienylmethyl]

N-[(1-(2-Thienylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2 a]indole-10-carboxamide (E7)

The title compound was prepared by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 2-(chloromethyl)thiophene using the procedure described in Example 1.

^{1}H NMR($CDCl_3$)

δ: 8.32(d,1H), 6.85-7.35(m,6H), 6.55(bt,1H), 4.52(t,2H), 4.10(t,2H), 3.74(s,2H), 3.32(t,2H), 2.90-3.05(m,2H), 2.25-2.50(m,4H), 1.30-1.90(m,5H).

Example 8 [X = (g), X^g = O, A = $(CH_2)_4$, (R_1^g , R_2^g, R_3^g, R_4^g= H; Y = NH, Z = 4-piperidinylmethyl, R_a = 2-(cyclohexyl)ethyl]

N-[(1-(2-(Cyclohexyl)ethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (E8)

The title compound was prepared by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 2-cyclohexylethyl bromide using the procedure described in Example 1.

^{1}H NMR($CDCl_3$)

δ: 8.28(d,1H), 7.10-7.35(m,3H), 6.64(t,1H), 4.57(t,2H), 4.13(t,2H), 3.22-3.44(m,4H), 2.65-2.80(m,2H), 2.30-2.55(m,4H), 1.55-2.05(m,12H), 1.10-1.35(m,4H), 0.85-1.05(m,2H).

Example 9 [X = (g), X^g = O, A = $(CH_2)_4$, (R_1^g , R_2^g, R_3^g, R_4^g= H; Y = NH, Z = 4-piperidinylmethyl, R_a = 1-naphthylmethyl]
N-[(1-(1-Naphthylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (E9)

The title compound was prepared by treating a solution of N-(4-piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (D2) and triethylamine in acetonitrile and N,N-dimethylformamide with 1-bromomethylnaphthylene using the procedure described in Example 1.
^{1}H NMR ($CDCl_3$)
δ: 8.23-8.48(m,2H), 7.70-7.90(m,2H), 7.33-7.57(m,4H), 7.00-7.30(m,3H), 6.52(t,1H), 4.46(t,2H), 4.01(t,2H), 3.90(s,2H), 3.31(t,2H), 2.90-3.07(bd,2H), 2.22-2.40(m,2H), 2.07(bt,2H), 1.55-1.85(m,3H), 1.20-1.50(m,2H).

Example 10 [X = (d), X_1-$(CH_2)_x$-X_2 = O-$(CH_2)_2$-O, R_1^d = NH_2, R_2^d = Cl, R_3^d = H, R_4^d, R_5^d = H; Y = O, Z = 4-piperidinylmethyl, R_a = 2-carboethoxyethyl]
[1-(2-Carboethoxyethyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate (E10)

4-Piperidinylmethyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate (0.100g; 0.31mmol) was dissolved in acetone (10ml) and treated with ethyl acrylate (0.037ml, 0.34mmol). The solution was heated at reflux (18 hours), cooled and evaporated *in vacuo* to a dark brown gum. The gum was purified by flash silica gel chromatography with $CHCl_3$→2% MeOH/$CHCl_3$ as eluant to yield the title compound as a colourless oil (0.053g; 41%) which was covered to the oxalate salt, mp=176-178°C.
^{1}H NMR (270MHz, CD_3OD) (oxalate salt)
δ:7.40 (s, 1H), 4.27 (s, 2H), 4.20-4.10 (m, 2H), 3.60-3.50 (d, 2H), 3.37 (t, 2H), 3.27-3.23 (m, 6H), 3.10-2.90 (t, 2H), 2.85 (t, 2H), 2.10-1.90 (d, 2H), 1.70-1.55 (m, 1H), 1.30-1.20 (m, 3H)

Example 11 [X = (d), X_1-$(CH_2)_x$-X_2 = O-$(CH_2)_2$-O, R_1^d = NH_2, R_2^d = Cl, R_3^d = H, R_4^d, R_5^d = H; Y = O, Z = 4-piperidinylmethyl, R_a = 3-hydroxybutyl]
[1-(3-Hydroxybutyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4,benzodioxan-5-carboxylate (E11)

a) 4-Piperidinylmethyl 8-amino-7-chloro-1,4-benzodioxan-5-carboxylate (0.100g; 10.31mmol) was dissolved in acetone (10ml) and treated with triethylamine (0.043ml; 0.31mmol) and methyl vinyl ketone (0.026ml; 0.34mmol). The solution was heated at reflux (18 hours), cooled and evaporated *in vacuo* to a yellow gum. The gum was purified by flash silica-gel chromatography with $CHCl_3$ as eluant to

yield [1-(3-oxobutyl)-4-piperidinyl]methyl 8-amino-7-chloro-1,4-benzodioxan-5-carboxylate as a colourless gum (0.050g; 41%) which was converted to the oxalate salt.

m.p. 160°C (Dec)

^{1}H NMR (250 MHz, $CDCl_3$) (Free base)

δ: 7.47 (s, 1H), 4.47 (s, 2H), 4.40-4.30 (m, 4H), 4.10 (d, 2H), 2.90 (d, 2H), 2.65 (s, 4H), 2.17 (s, 3H), 2.00 (t, 2H), 1.85-1.70 (m, 2H), 1.47-1.25 (m, 3H)

b) [1-(3-oxobutyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4,benzodioxan-5-carboxylate (0.135g, 0.340mmol) (was dissolved in EtOH (8ml) and treated with $NaBH_4$ (0.013g, 0.340mmol) with stirring. After 1h, the reaction mixture was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 and water. The aqueous layer was then extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil, which was purified by silica-gel chromatography (CH_2Cl_2/10% MeOH as eluant) to give the title compound as a colourless oil (0.048g, 35%), which was converted to its oxalate salt m.p. 220-220°C.

^{1}HNMR (200MHz, $CDCl_3$) (free base) δ7.50 (s, 1H), 4.50 (s, 2H), 4.35 (s, 4H), 4.10 (d, 2H), 3.96 (m, 1H), 3.25 (d, 1H), 3.00 (d, 1H), 2.65 (m, 2H), 2.18 (t, 1H), 2.00-1.35 (m, 9H), 1.20 (d, 3H).

Descriptions

Description 1

(1-Benzyl-4-piperidinyl)methylamine(D1)

A stirred solution of isonipecotamide (30.1g, 0.23 mole) and benzyl bromide (27.9 ml, 0.23 mole) in ethanol (250 ml) was treated with anhydrous potassium carbonate (64.9g, 0.47 mole) and heated under reflux for 3h. The mixture was allowed to cool, then filtered and the filtrate concentrated under vacuum. The residual oil was dissolved in chloroform (200 ml) and washed with water (1 x 150 ml), then dried (Na_2SO_4) and concentrated under vacuum to leave a yellow solid (41.0g). This solid was mixed thoroughly with phosphorus pentoxide (38.3g, 0.27 mole) and the mixture heated at 180°C under nitrogen for 2.5h with gentle stirring. The reaction mixture was allowed to cool, then treated with water (300 ml). When the solid mass had dissolved, the solution was basified by addition of solid K_2CO_3 and extracted with ethyl acetate (2x250 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to leave a brown oil (35.3g). This was dissolved in dry ether (250 ml) and added dropwise over 30 minutes to a stirred suspension of lithium aluminium hydride (10.1g, 0.26 mole) in ether (150ml) at 0°C

under nitrogen. When addition was complete, the mixture was allowed to warm up to room temperature and was stirred for 1.5h. It was re-cooled to 0°C and treated cautiously with water (10ml), 10% NaOH solution (15 ml) and water again (25ml). The mixture was filtered through kieselguhr and the filtrate concentrated *in vacuo* to leave a brown oil, which was distilled under vacuum to afford the title compound as a colourless oil after distillation (27.8g, 67%) bp 106°C at 0.25 mmHg.

^{1}H NMR ($CDCl_3$)

δ: 7.20-7.37(m,5H), 3.48(s,2H), 2.85-2.95(m,2H), 2.55(d,2H), 1.87-2.00(m,2H), 1.60-1.75(m,2H), 1.10-1.40(m,5H).

Description 2

a) N-[(1-Benzyl-4-piperidinyl)methyl] indole-3-carboxamide

To a stirred solution of indole-3-carboxylic acid (15g, 0.093mole) in dichloromethane (250 ml) under nitrogen was added oxalyl chloride (8.7 ml, 0.10 mole) and dry dimethylformamide (6 drops). After 2 hours, the solvent was evaporated under reduced pressure. The residual acid chloride (0.093 mole) was dissolved in dichloromethane (100 ml) and added dropwise to a stirred solution of N-(1-benzyl-4-piperidinyl)methylamine (D1, 16.4g, 0.093 mole) and triethylamine (15.5 ml, 0.11 mole) in dichloromethane (150 ml) at 5°C. After stirring at ambient temperature overnight, the reaction mixture was washed with 10% Na_2CO_3 and the organic phase was dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residual solid recrystallised from ethyl acetate to afford the title compound as a white solid (17.5g, 60%).

^{1}H NMR ($CDCl_3$)

δ: 9.90(s,1H), 7.85-7.95(m,1H), 7.64(d,1H), 7.15-7.43(m,8H), 6.17(t,1H), 3.48(s,2H), 3.37(t,2H), 2.83-2.98(m,2H), 1.87-2.08(m,2H), 1.54-1.82(m,3H), 1.23-1.50(m,2H).

b) N-[(1-Benzyl-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide

A stirred suspension of N-[(1-benzyl-4-piperidinyl)methyl] indole-3-carboxamide (17.5g, 0.050 mole) in chloroform (250 ml) was treated with 3-bromo-1-propanol (10.1 ml, 0.11 mole) and N-chlorosuccinimide (8.7g, 0.065 mole) at room temperature and a clear solution was obtained in 15 minutes. After 1h the reaction mixture darkened in colour from pale yellow to orange and temperature rose to 38°C. After a further 1 h the reaction mixture was treated with 10% $NaHCO_3$ solution and the chloroform layer separated, dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil, which was chromatographed on silica gel eluting with 3% methanol/chloroform. The 2-(3-bromopropoxy)indole intermediate was dissolved in

acetone (400 ml), treated with anhydrous potassium carbonate (11g, 0.08 mole) and stirred at room temperature for 20h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (200 ml) and extracted with chloroform (2 x 250 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with 5% methanol/chloroform to afford the title compound as a pale yellow oil (3.1g, 15%). This was converted to its oxalate salt and crystallised from acetone as a white solid mp 169-170°C.

Free base:- ^1H NMR ($CDCl_3$)

δ: 8.32(d,1H), 7.05-7.38(m,8H), 6.53(t,1H), 4.50(t,2H), 4.08(t,2H), 3.48(s,2H), 3.31(t,2H), 2.83-2.97(m,2H), 2.27-2.41(m,2H), 1.54-2.06(m,5H), 1.25-1.45(m,2H).

c) N-(4-Piperidinylmethyl) 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide

A stirred suspension of N-[(1-benzyl-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide oxalate salt (2.25g, 0.0046 mole) in ethanol (100 ml) and glacial acetic acid (4 ml) was hydrogenated over 10% Pd-C (0.8g) at atmospheric pressure and 45°C for 18h. The mixture was filtered and the filtrate concentrated *in vacuo*. The majority of the product was in the solid which had been filtered off. This material was shaken with concentrated potassium carbonate solution (50 ml) and chloroform (50 ml) together with the residue from the filtrate. The mixture was filtered, the chloroform layer separated and dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound (D2) as a white solid (1.52g, 100%). This was recrystallised from chloroform/60-80 petrol mp 139-141°C.

^1H NMR ($CDCl_3$)

δ: 8.32(d,1H), 7.03-7.30(m,3H), 6.53(t,1H), 4.48(t,2H), 4.05(t,2H), 3.30(t,2H), 3.02-3.15(m,2H), 2.52-2.70(m,2H), 2.27-2.40(m,2H), 1.65-1.90(m,4H), 1.10-1.30(m,2H).

Description 3

4-Piperidinylmethyl 8-amino-7-chloro-1,4-benzodioxan-5-carboxylate hydrochloride

a) To a stirred solution of 8-amino-7-chloro-1,4-benzodioxan-5-carboxylic acid (prepared from the corresponding 7-H acid (prepared as in GB 1571278) by chlorination of the protected form) (1.10g) in acetonitrile was added bis-carbonyldiimidazole (0.77g). The reaction mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure to afford crude 8-amino-7-chloro-1,4-benzodioxan-5-imidazolide.

b) To a solution of N-*tert*-butoxycarbonyl-4-hydroxymethyl piperidine (0.25g) in dry THF (10ml) was added methyllithium (1.5M in diethylether; 0.78ml) at 0°C under a nitrogen atmosphere. Stirring was continued at ambient temperature for 10

min. 8-Amino-7-chloro-1,4-benzodioxan-5-imidazolide (0.33g) in THF (10ml) was added to the reaction mixture and stirring continued for 2 hours. The reaction mixture was cooled to 0°C and water was added. The solvent was removed under reduced pressure and the residue partitioned between chloroform and water. The organic phase was washed with water (3x), dried (Na_2SO_4) filtered and concentrated *in vacuo*. Flash chromatography on silica using chloroform and ethanol as eluant gave the title compound (0.26g).

^1H NMR 250MHz ($CDCl_3$)

δ: 7.47(s,1H), 4.49(s,2H), 4.36(s,4H), 4.08-4.22(m,4H), 2.64-2.80(m,2H), 1.84-2.01(m,1H), 1.70-1.83(m,2H), 1.46(s,9H), 1.18-1.38(m,2H)

c) HCl(g) was bubbled into a cooled solution of 8-amino-7-chloro-(N-*tert*-butoxycarbonyl-4-piperidylmethyl)-1,4-benzodioxan-5-carboxylate (0.26g) in dioxan (50ml) for 25 min. The solvent was concentrated *in vacuo* and the residue triturated with Et_2O to afford pure title compound (0.12g).

mp 249-251°C

^1H NMR 250MHz (DMSO)

δ: 8.99-9.10(m,1H), 8.59-8.78(m,1H), 7.29(s,1H), 5.73(s,2H), 4.25-4.34(s,4H), 4.03(d,2H), 3.20-3.42(m,2H), 2.75-2.97(m,2H), 1.76-2.06(m,3H), 1.48-1.57(m,2H)

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A

compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

The compounds tested had a pIC_{50} of >7, E1 had a pIC_{50} of >9.

2) Rat oesophagus

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100µM for 15 min followed by washout) and in the presence of cocaine (30µM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3µM).

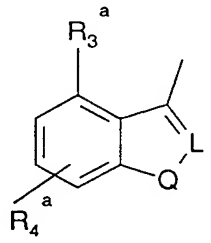
Claims

1. Compounds of formula (I) and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

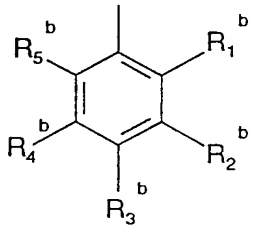
X-CO-Y-Z (I)

wherein

X is a monocyclic or polycyclic aromatic group, such as a group of formula (a), (b), (c), (d), (e), (f) or (g):



(a)



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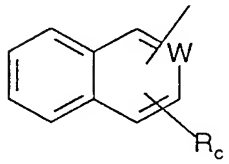

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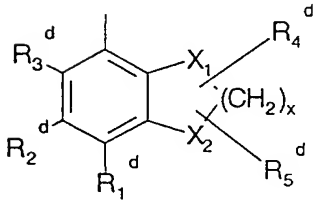

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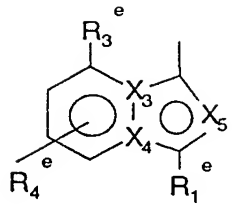

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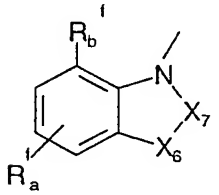

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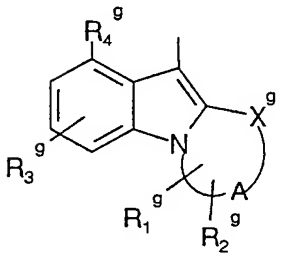


(g)

wherein

L is N or CR_S wherein R_S is hydrogen, C_{1-6} alkoxy, halogen, C_{1-4} alkyl or cyano;

Q is NR_1^a, CH_2, O or S;

W is CH or N;

in which X_1-$(CH_2)_X$-X_2 forms a 5-7 membered ring wherein X_1 is O or S; X_2 is O, S, NR or NRCO wherein R is hydrogen or C_{1-6} alkyl; and

x is 1, 2 or 3;

one of X_3 and X_4 is N and the other is C; and

X_5 is N or CR wherein R is hydrogen, C_{1-6} alkoxy, halo, C_{1-6} alkyl or cyano;

R_1^a is hydrogen, C_{1-10} alkyl, C_{2-6} alkenyl, aralkyl, C_{2-6} alkanoyl or C_{2-6} alkanoyl C_{1-3} alkyl;

R_3^a is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkoxy;

R_4^a is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R_1^b is C_{1-6} alkoxy; and

R_2^b is hydrogen, chloro or fluoro;

R_3^b is hydrogen,C_{1-6} alkyl, amino optionally substituted by a C_{1-6} alkyl group, halo, hydroxy or C_{1-6} alkoxy;

R_4^b is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio; and

R_5^b is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_c is hydrogen, C_{1-6} alkoxy, halo or C_{1-6} alkyl;

R_1^d is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2^d is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3^d is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4^d and R_5^d are independently hydrogen or C_{1-6} alkyl;

R_1^e is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkyl C_{1-4} alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups;

R_3^e is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkyl;

R_4^e is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

X_6-X_7 is NR_z-CO or $CR_1^fR_2^f$-$CR_3^fR_4^f$ where

R_z and R_1^f to R_4^f are independently hydrogen or C_{1-6} alkyl; and/or

R_1^f/R_2^f and R_3^f/R_4^f together are a bond and/or $R_1^f/R_2^f/R_3^f/R_4^f$ are joined to form C_{3-6} polymethylene;

R_a^f is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkyl;

R_b^f is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

X^g is O, S, SO, SO_2, CH_2, CH, N or NR wherein R is hydrogen or C_{1-6} alkyl;

A is a saturated or unsaturated polymethylene chain of 2 - 4 carbon atoms;

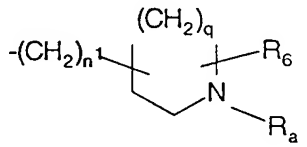
R_1^g and R_2^g are hydrogen or C_{1-6} alkyl;

R_3^g is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkoxy;

R_4^g is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

Y is O or NH;

Z is of sub-formula:



wherein

$-(CH_2)_n{}^1$ is attached at carbon; and

n^1 is 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

R_a is straight or branched chain alkylene of chain length 1-6 carbon atoms terminally substituted by R_7 wherein and R_7 is aryl, 3 to 8 membered cycloalkyl, 3 to 8 membered heterocyclyl, 5 or 6 membered monocyclic heteroaryl or 9 or 10 membered fused bicyclic heteroaryl linked through carbon, or R_7 is

C_{2-7} alkoxycarbonyl or secondary or tertiary hydroxy substituted C_{1-6} alkyl; and

R_6 is hydrogen or C_{1-6} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

2. A compound according to claim 1 wherein:

L in formula (a) is C-H, C-CH_3, C-Cl or C-OCH_3;

Q in formula (a) is $NR_1{}^a$;

$R_1{}^a$ is hydrogen or a methyl or ethyl group.

3. A compound according to claim 1 wherein:

$R_1{}^b$ is methoxy;

$R_3{}^b$ is amino;

$R_4{}^b$ is halo;

$R_5{}^b$ is hydrogen.

4. A compound according to claim 1 wherein:

X_1-$(CH_2)_x$-X_2 moiety is O-$(CH_2)_2$-O, O-$(CH_2)_3$-O, O-CH_2-O, O-$(CH_2)_2$-NR, O-$(CH_2)_2$-S or O-CH_2-CONR, wherein any of the methylene linkages are optionally mono- or di- substituted by C_{1-6} alkyl groups;

$R_1{}^d$ is hydrogen or amino;

$R_2{}^d$ is hydrogen or halo;

$R_3{}^d$ is hydrogen or halo.

5. A compound according to claim 1 wherein:

$R_1{}^e$ is CF_3 or an ethyl group;

X_5 is N, C-H or C-OCH_3;

$R_3{}^e$ is hydrogen;

$R_4{}^e$ is hydrogen or halo, such as iodo.

6. A compound according to claim 1 wherein:

X_6-X_7 when $CR_1{}^fR_2{}^f$-$CR_3{}^fR_4{}^f$ is CH_2-CH_2, CH=CH; NH-CO or NEt-CO;

$R_a{}^f$ is hydrogen;

$R_b{}^f$ is hydrogen or halo.

7. A compound according to claim 1 wherein:
A is $-CH_2-(CH_2)_r-CH_2-$ wherein r is 0, 1 or 2; $-CH_2-CH=CH-$; $-C(CH_3)=CH-$ or when X^g is CH or N, A may be $-(CH_2)_2-CH=$ or $-CH=CH-CH=$;
R_1^g and R_2^g are hydrogen or R_1^g and R_2^g are gem-dimethyl;
r is 1;
R_3^g is hydrogen;
R_4^g is hydrogen or halo.

8. A compound according to any one of claims 1 to 7 wherein Y is O or NH.

9. A compound according to any one of claims 1 to 8 wherein n^1 is 1 and the azacycle is attached at a 4-position carbon atom, when q is 2, and Z is 4-piperidinylmethyl and 4-pyrrolidinylmethyl, N-substituted by R_a as defined in claim 1.

10. A compound according to any one of claims 1 to 9 wherein Z is as in any of the Examples hereinbfore described.

11. 5-(1-(3-Pyridylmethyl)-4-piperidinyl)methyl-8-amino-7-chloro-1,4-benzodioxancarboxylate.

12. N-[(1-(4-Pyridylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

13. N-[(1-(2-(1-Piperidinyl)ethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

14. N-[(1-(Benzofuran-2-ylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

15. N-[(1-(Quinolin-2-ylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

16. N-[(1-(5-Phenylpentyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

17. N-[(1-(2-Thienylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

18. N-[(1-(2-(Cyclohexyl)ethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

19. N-[(1-(1-Naphthylmethyl)-4-piperidinyl)methyl] 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

20. [1-(2-Carboethoxyethyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate.

21. [1-(3-Hydroxybutyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate.

22. A compound according to any one of claims 7 to 10 in the form of a pharmaceutically acceptable salt.

23. A compound according to any one of claims 10 to 22 but wherein Y is NH.

24. A process for preparing the ester or amide compounds (where Y is O or NH) according to claim 1, which comprises reacting an appropriate acid derivative with an appropriate alcohol or amine.

25. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23, and a pharmaceutically acceptable carrier.

26. A compound according to claim 1 for use as an active therapeutic substance.

27. The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

28. The use according to claim 27 for use as a 5-HT_4 receptor antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

INTERNATIONAL SEARCH REPORT

Intern . al Application No
PCT/EP 93/03054

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D498/04 C07D405/14 C07D405/12 A61K31/535 A61K31/445
//C07D498/04,265:00,209:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 176 785 (ASTRA LAKEMEDEL) 7 January 1987 see claims 1,12,16	1,25,28
X	EP,A,0 407 137 (YOSHITOMI) 9 January 1991 see page 1; claims 1,5	1,25,28
P,X	WO,A,93 03725 (SMITH KLINE BEECHAM) 4 March 1993 cited in the application see page 49 see page 2 - page 3; claims 1,10	1,25,28
P,X	WO,A,93 05038 (SMITHKLINE BEECHAM) 18 March 1993 cited in the application see claims 1,11,16,17	1,25,28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 1994	18. 02. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 93/03054

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 18036 (SMITHKLINE BEECHAM) 16 November 1993 cited in the application see claims 1,12,15	1,25,28
A	EP,A,0 501 322 (GLAXO GROUP) 2 September 1992 cited in the application see claims 1,15,16	1,25,28

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/EP 93/03054

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2176785	07-01-87	NONE		
EP-A-0407137	09-01-91	CA-A-	2020315	04-01-91
		US-A-	5185333	09-02-93
		JP-A-	3279372	10-12-91
WO-A-9303725	04-03-93	NONE		
WO-A-9305038	18-03-93	AU-A-	2491092	05-04-93
		AU-A-	2541892	05-04-93
		WO-A-	9305040	18-03-93
		AU-A-	2435092	16-03-93
		AU-B-	3457293	03-09-93
		WO-A-	9316072	19-08-93
		WO-A-	9324117	09-12-93
		WO-A-	9400113	06-01-94
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EP-A-0501322	02-09-92	AU-B-	645402	13-01-94
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		WO-A-	9214727	03-09-92